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Health Consulting
Issues Management
Research and Data Analysis

June 7, 2004

Division of Dockets Management
(HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

http://www.fda.gov/dockets/ecomments

Re: Docket No. 2004D-0188: Development and Use of Risk Minimization Action Plans

These comments are submitted in response to the May 5th, 2004, *Federal Register* Notice requesting comments on draft guidance for industry on development and use of risk minimization action plans (RiskMAPs) [Docket No. 2004D-0188], 69 FR 25130.

This draft guidance, in combination with the guidances on premarketing risk assessment and good pharmacovigilance practices and pharmacoepidemiologic assessment, provides a reasonable conceptual path for drug development by assessing risks and benefits, developing and testing risk mitigation, and providing for monitoring as appropriate to control risks throughout the lifecycle of a drug. At the same time, the guidance also leaves many questions unresolved, perhaps deliberately. We at PinneyAssociates suggest that the process of clarification continue throughout the lifecycle of these guidances.

1 Risk Benefit Ratio

All drugs have potential risks as well as potential benefits and thus determining whether the risk benefit ratio is acceptable is critical in determining the approvability of a new drug. As noted in the guidance, benefits and risks are "usually measured in different units" (line 133). More relevant, perhaps, is that any assessment of the risk benefit ratio relies on objectively defined and quantified benefits in comparison with uncertain and often theoretical risks. These abstract risks appear to carry equal or greater weight in decision making. This will clearly be an area in which human judgment and perhaps expert advisory committee review will be critical. We suggest that the agency directly address the apparent unequal weighting of risks and benefits.

2 Determining When a RiskMAP Should Be Considered

The draft guidance specifically identifies "Schedule II controlled substances, including Schedule II extended release or high concentration opiate drug products" as appropriate products for RiskMAPs (lines 225-228). This gives the appearance of minimizing the importance that RiskMAPs may have for other Schedule II drugs, such as sedatives, tranquilizers, and stimulants. Although RiskMAPs may be most applicable for Schedule II drugs, they may often be appropriate for Schedule III drugs, some Schedule IV, V, and even unscheduled drugs. RiskMAPs may be particularly important for these drugs if/when they are formulated into extended release or high concentration products, and we believe that these points are important to elucidate in the guidance.

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We also understood these lines to refer to all "opioids" (opium-derived as well as semi-synthetic and synthetic drugs), not just "opiates" (opium-derived drugs only), and suggest that FDA clarify the terminology for the benefit of all sponsors.

A statement is needed to clarify that these standards apply to both innovator and generic drug products, enabling generic companies to factor development of a RiskMAP into their investment decisions. There is no reason to believe that risks are more highly associated with the innovator drug than with the generic drug. For drugs of abuse, the exact opposite may be true. Because the generic forms are almost always less expensive, the number of prescriptions often increases, increasing the supply of drug for diversion, and decreasing the cost of the diverted drug of abuse, which in turn encourages additional abuse. If this guidance does not apply to the generic forms of a drug, then at the time of generic introduction, the sponsor of the innovator drug should be permitted to alter the RiskMAP to reflect that of the generic drug product. Along this same theme, we recommend that FDA progress towards consistency across drugs within a class, and ask that FDA clarify if an equivalent RiskMAP is required for all similar drugs in a category when a RiskMAP is required for one specific drug.

In addition to innovator and generic drug products, we believe that this guidance should apply to both newly marketed drugs and older drugs as risk issues are identified (e.g., abuse of some of the older opioids has been increasing over the past several years and yet hydrocodone products, for example, do not have RiskMAPs.) Because the guidance is "something that is suggested or recommended, but not required" (lines 14-15), this would allow for RiskMAPs to be developed for older drugs as risk issues arise.

We ask that the Agency clarify its view on these issues and develop a plan for consistency.

3 Relationship Between RiskMAP and Scheduling Decisions

We suggest that the development of a RiskMAP presents an opportunity to discuss any relationship between the RiskMAP and drug scheduling decisions for drugs potentially regulated under the provisions of the Controlled Substances Act. In addition, a good RiskMAP may suggest that less restrictive scheduling of a drug can be maintained or that an extended release formulation, where the total opioid content per dose exceeds the general guidelines, should not be more restrictively scheduled than other formulations.

4 RiskMAP Evaluation

4.1 Unintended consequences

There needs to be more discussion on how to address "potential unintended consequences" (line 444). For example, if it is found that physicians are continuing to prescribe an older drug (with less clinical benefit and/or greater risks) instead of a new drug because of the RiskMAP requirements, then the RiskMAP needs to be reassessed quickly and revised as needed. Alternatively, a RiskMAP for the older drug may need to be considered.

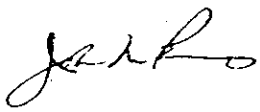
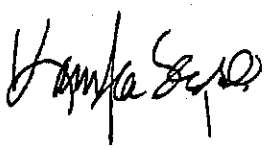
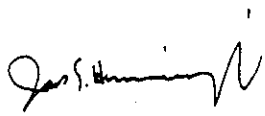
4.2 FDA assessment of RiskMAP evaluation results

Details about how FDA will utilize its own results (lines 605-613), especially if they differ from the sponsor's interpretation, need to be included in this section. For example, in what timeframe will these analyses be done? With whom will the results be communicated? If there is disagreement between the FDA results and the sponsor's results, how will differences be reconciled?

4.3 Making information from RiskMAP evaluations available to the public

The draft guidance notes that information about the effectiveness of RiskMAP tools will be released to the public on a RiskMAP Web site (lines 617-626). It is unclear what type of information would be available, in what timeframe it would be released, and how it would be released. In addition, will the information first be communicated to the drug's sponsors for comment? Will the sponsor have any input into what will be released? If information from one company indicates an issue with another company's drug, will that be communicated to the other drug company prior to the release of information to the public?

Respectfully submitted,

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